Review
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Imaging Modalities for Adrenal Lesions

Adrenal Lezyonlarda Görüntüleme Yöntemleri

Imaging in Adrenal Lesions

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Özet

Adrenal bezler insan fizyolojisinde çok önemli bir role sahiptir. Küçük boyutlarına rağmen birçok benign ve malign lezyonun hedefi olabilirler. Görüntüleme yöntemlerindeki gelişmeler sonucu rastlantısal olarak saptanan adrenal lezyonların sayısı artmaktadır. Adrenal insidentalomaların görüntüleme yöntemleri ile benign-malign ayrımının yapılabilmesi, uygun tedavi seçeneğinin belirlenmesi ve gereksiz invasiv yöntemlerin önüne geçilebilmesi için gereklidir. Bu ayrımın yapılmasında tüm görüntüleme yöntemleri için çeşitli kriterler belirlenmiştir. Ancak zaman zaman benign ve malign lezyon özellikleri üst üste binebilir ve ayrım zor olabilir. Görüntüleme yöntemleri birbirini tamamlayacak şekilde kullanılmalı ve seçilecek yönteme hastanın klinik-laboratuvar öyküsü baz alınarak karar verilmelidir.

Anahtar Kelimeler

Adrenal Lezyon; Benign; Malign; Görüntüleme Yöntemi

Abstract

The adrenal glands have a unique role in the physiological regulation of the human body. Although they are very small, the adrenal glands can be affected by many benign and malign lesions. Through the improvements in imaging modalities, determination of adrenal incidentalomas has substantially increased. The differentiation of benign adrenal lesions from malign lesions is very important to determine the appropriate management and to avoid unnecessary invasive tests. For this differentiation, various criteria have been determined for all imaging modalities. But, sometimes benign and malign lesions may overlap and the differentiation can be very difficult. The imaging modalities should be used to complement each other and the choice of imaging modality must be based on the clinical and laboratory histories of patients.

Keywords

Adrenal Lesions; Benign; Malignant; Imaging Modalities.

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Introduction

The adrenal glands have a unique role in the physiological regulation of the human body. Although they are very small, the adrenal glands can be affected by many benign and malign lesions. Adrenal masses can be primary or secondary, functioning or non-functioning, and arising from the cortical or medullary region [1].

Through improvements in imaging modalities and protocols, determination of adrenal lesions has substantially increased. Adrenal nodules are seen in 9% of the human population;the majority of them are detected by chance during abdominal imaging for other problems and are termed incidentalomas [2]. Most of the adrenal lesions are adenomas [3]. In contrast, adrenocortical carsinoma (ACC) is rare. The risk of ACC is 2-6% for lesions 4-6 cm in diameter but <2% forlesions smaller than 4 cm [4]. A meta-analysis that includes 110 articles between 1980-2008 estimates the rate of ACCs among incidentally discovered adrenal masses to be 1.4% median [5]. Although the prevalence of ACC is very low in the population without known malignancy, in patients with malignancy history, the possibility of an adrenal lesion being malignant is nearly 25-36% [6].

The imaging of adrenal lesions is very important in order to differentiate benign (e.g. adrenocortical adenoma, myelolipoma, cyst, and hemoragy) from suspicious lesions (e.g. pheochromocytoma, metastasis, ACC, and adrenal lymphoma), to determine the appropriate management and to avoid unnecessary invasive tests.

Imaging Modalities

1. Ultrasonography (US): US is the most widespread technique for the evaluation of abdominal pathologies. It is simple, inexpensive, easily available, and radiation free. Although the visualization of adrenal glands is difficult with US, especially in obese patients, it still has a role in incidentally detecting adrenal masses. US is more appropriate for infants and children than adults [1,7].

2.Computed tomography (CT): CT is the primary imaging method for the detection and characterization of adrenal lesions. Both nonenhanced CT and multiphase contrast-enhanced CT (MPCT) have a role in adrenal imaging. On nonenhanced CT, an attenuation of fewer than 10 Hounsfield units (HU) suggests a diagnosis of adenoma and no further evaluation is necessary. Also, the presence of macroscopic fat supports the diagnosis of myelolipoma, a benign process [8].

CT histogram is a technique that is based on the intracytoplasmic lipid content of adenomas. It plots the attenuation value of each pixel in the region of interest (ROI) with respect to its frequency. The number of negative pixels in ROI corresponds to the amount of lipid content. Nearly 97% of adenomas contain negative pixels, but metastasis does not have negative pixels [9].

MPCT protocols include nonenhanced scan, contrast-enhanced scan at portal venous (PV) phase (65. second) and delayed phase (DP) at 15. minute [9]. Both adenomas and malignant lesions show rapid enhancement after contrast injection, but adenomas show more rapid washout than malign lesions. The calculation of absolute percent washout (APW) and relative percent washout (RPW) helps in distinguishing benign adenomas from malign lesions.

The formula of APW is x 100

The formula of RPW is x 100

If there is a greater washout with a generally accepted threshold of ≥60% APW, the lesion is presumably benign. Also if the RPW values ≥40%, the lesion is more likely benign [10].

3. Magnetic resonance imaging (MRI): Normal adrenal has homogeneous, low to intermediate signal intensity on T1 and T2-weighted sequence. In chemical shift imaging (CS), adenomas indicate signal loss on the out-phase images. The signal loss can be noticed visually or can be evaluated by calculating the adrenal-splenic ratio (ASR) and signal intensity index (SII) [9,11].

ASR= x 100

SII= x 100

The value of ASR < 70% is 78% sensitive for adenoma and 11-16% of intensity loss in SII can determine adenomas and metastasis accurately [9]. For lipid-rich adenomas the accuracy of CS MRI is similar to CT but CS might be superior for lipid-poor adenomas [1].

MRI is also useful for determination of pheochromocytoma. On T2-weighted images, pheochromocytoma has intermediate to high signal frequently but the classic 'light bulb bright' T2 appearance is seen in only approximately 30% of cases [10].

For differentiation of benign and malign lesions, size, border/internalcharacteristic of lesion, and elongation to adjacent structures are also very important. Malign lesions tend to be larger than benign lesions. A threshold of 4 cm can be used to determine benignity or malignity with higher than 90% sensitivity [6]. Additionally, heterogenity, irregular border, and inferior vena cava invasion are indicators for malignancy.

The radiological features that can be used in determination of benign and malign lesions are summarized in Table 1 [9]. These features can be directive for determination of benign and malign lesions only; they can not provide certainty.

Table 1. Radiological features of benign and malign adrenal lesions [9]

	BENİGN	MALİGN (ACC or METASTASİS)
Size	< 4 cm	>4 cm
Shape/Border	Round/regular	Thick/irregular
Homogeneity	Homogeneous	Heterogeneous
Lipid rate	High (excluding lipid poor adenomas)	Low
Growth rate	Slow	Rapid
Density in CT	< 10 HU (lipid rich ones) >10 HU (lipid poor ones)	>10 HU
Enhancement pattern	Rapid enhancement, rapid washout	Different enhancement, slow washout
APW	>60%	< 60%
RPW	>40%	<40%
MRI signal in T2	Low	High
Signal loss in out-phase	>30%	<30%
ASR	< 70%	>70%
SII	>5%	<5%

4. Positron emission tomography (PET) and PET CT: PET is a very useful modality for determination of benign and malign lesions. If the uptake of 18F-fluorodeoxyglucose (FDG) is higher in

adrenal than liver, the lesion should be considered malign. PET CT combines density values on nonenhanced CT with functional activity. PET CT can show 5% false positive results because of functioning adenomas and inflammatory situations like sarcoidosis and tuberculosis. Also false negative results can be seen in metastasis from which primary do not show substantial FDG uptake, such as bronchioalveolar carcinoma and carsinoid tumor [1,9]. I-131 Metaiodobenzilguanidin (MIBG) scintigraphy can also be used to localize pheochromocytomas [12].

In literature there are many studies which compare the efficiencies of imaging modalities for determination of adrenal masses. Tian et al. [13] analyzed the CT findings of greater than 5 cm adrenal adenomas and discussed if it were possible to differentiate large adenomas from adrenal carcinoma. They found that the shape, border of mass, and heterogenity had no significance for identification of both entities. The only valuable identification between large adenomas and carcinoma was local invasion and distant metastasis. Park et al. [14] found the sensitivity was 45.7% and specificity was 97.1% with the nonenhanced CT at a cut-off value of 10 HU, but using the APW value at a cut-off of 55%, the sensitivity was 93.9%and the specificity was 95.8%. These results show that washout CT is very important for differentiation of lipid poor adenomas from nonadenomas. A study that included 53 adenomas (30 lipid rich, 23 lipid poor) and 15 nonadenomas showed that the threshold value of 10 HU on nonenhanced CT gave 100% accuracy for lipid rich adenomas but 57% sensitivity for total adenomas because of the presence of lipid poor adenomas. Also in this study, APW showed 78% sensitivity and 100% specificity and the highest accuracy (87%). When they took the threshold value of 19 HU instead of 10 HU on nonenhanced CT and >45% instead of >60% for APW, the sensitivity increased to 94% [15].

Park et al. [16] reported that ROI size and location were also very important factors for the sensitivity of CT especially to differentiate large adenomas from carcinoma; a ROI covering more than half of a lesion should be used.

A study which compares CT washout with CS MRI found that CT APW had high sensitivity (84%), specificity (79%), and accuracy (83%) to MRI SII calculations (67%, 89%, 74%) [17]. Another study about lipid poor adrenal adenomas showed that MRI sensitivity for 10HU-20HU adrenal adenomas is 100%, but it decreased to 64% for greater than 20 HU lesions, 61.5% for greater than 30 HU lesions, and 40% for greater than 40 HU lesions. Their study also showed that washout CT was more accurate than CS MRI for lipid poor adenomas [18].

CT histogram is a technique based on the intracytoplasmic lipid content of adenomas. Jhaveri et al. [19] compared CT histogram analysis and CS MRI for indeterminate adrenal lesions using a 10% negative pixels threshold on nonenhanced CT and 20% signal intensity drop in CS MRI. The sensitivity of CT histogram for diagnosing adenoma was 46%, while the sensitivity of CS MRI was 71%. But another study which consisted of 67 adenomas and 42 metastases showed that all of the adenomas contained negative pixels on nonenhanced CT. 50% of metastases also contained negative pixels; however, none of them had more than 10% negative pixels. Unlike the previous study, the CT histogram analysis using a 10% negative pixel threshold had a 91% sensitivity and 100% specificity. Using an ASR ratio of less than 0.71 and SII of more than 16.5, MRI's sensitivity was 97% [3]. Remer et al. [20] reported that using a 10% negative pixel threshold CT histogram analysis had 88% specificities for nonenhanced CT and 99% specificities for enhanced CT. Despite these values, the sensitivity was very low (71% for nonenhanced CT, 12% for enhanced CT). In a study by Ho et al. [21], 132 adrenal nodules in patients with lung carcinoma were analyzed for distinction of adenomas from metastases on nonenhanced CT. Using a threshold of 10 HU density, sensitivity was 68% and specificity was 100% for the diagnosis of edenomas. When CT histogram analysis using a threshold of 10% negative pixel was performed, the sensitivity increased to 84% and the specificity remained the same. Based on these results, it can be said that CT histogram analysis may be superior to nonenhanced CT for the diagnosis of adenomas, but that it does not make a significant contribution to washout CT and CS MRI.

Joakim et al. [22] compared CT, MRI, and ^{11}C-metomidate (MTO PET) for evaluation of adrenal incidentalomas. They reported that sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for MTO PET was 100%. For MRI, the values were 86%, 100%, 100%, 50% and for CT, 71%, 100%, 100%, 33%. The highest sensitivity was found by MTO PET. But, CT and MRI could not correctly characterise 2 adenomas of 24 incidentalomas; however, these 2 adenomas were correctly determined by MTO PET. This study concluded that because PET was an expensive modality, it was not suitable as an initial imaging method. Also, MTO PET produced very limited extra information. For these reasons, CT and/or MRI should be preferred for first-line evaluation.

Maurea et al. [23] compared T1-T2 weighted images, CS images, and T1 sequence after gadolinium-DTPA (Gd) images to evaluate the diagnostic accuracy of adenomas and nonadenomas. Diagnostic criteria for adenomas were iso-hypointensity on both T1-T2 sequences, signal loss on out-of-phase CS images and mild transient enhancement after Gd. They found the accuracy 80%, sensitivity 72% , 100% specificity, 100% PPV, 60% NPV for T1-T2 sequences and 93% , 90%, 100%, 100%, 80% for CS and T1-Gd images. This study indicated that the use of CS and T1-Gd images increased the sensitivity and accuracy and reduced the false negatives in the identification of adrenal adenomas compared with conventional T1-T2 sequences. Because of the clear diagnostic role of CS MRI in the determination of adrenal adenomas, the need for T1-Gd sequences could be obviated.

Mauera et al. [24] compared MRI and radionuclide techniques in their study for definition of non-hypersecreting adrenal masses. They included 30 non-hypersecreting adrenal masses of which 22 lesions were benign and 8 lesions were malign. They applied both MRI and adrenal scintigraphy using appropriate radiopharmaceuticals (norcholesterol scintigraphy, iodine-131 MIBG, FDG PET). 46% of adenomas had hyperintense signal on T2 images, 92% of adenomas had no significant lesion enhancement, and 100% of them had signal intensity loss on out-phase CS images. In patients with pheochromocytomas, T2 hyperintensity and significant lesion enhancement occured in all cases and none of the lesions showed signal intensity change on out-phase images. Of the adrenal malign lesions, 100% had T2 hyperintensity, 63% showed significant lesion enhancement, and signal intensity loss on out-phase CS images was observed on none of them. The results of nuclear studies were: 100% of adenomas showed increased norcholesterol uptake, 100% of pheochromocytomas showed abnormal MIBG activity, and 100% of malignant adrenal tumors had increased FDG uptake. Based on these results, it can be said that T2 hyperintensity and Gd-enhanced MR images have limited utility in distinguishing adenomas from non-adenomas. CS MRI images have significant importance for

determination of adenomas but their efficacy is restricted for lipid poor adenomas. The results of this study showed radionuclide studies had a more substantial contribution for adrenal lesion characterization than MRI. Maurea et al. [25], in another study that included more lesions, found similar results..

Leboulleux et al. [26] compared PET/CT and CT for the diagnosis of ACC. They reported PET/CT and CT had similar sensitivity for diagnosis of ACC and ACC metastases but that PET/CT was superior to CT for the detection of local relapses.

A study consisting of a large series, all pathologically confirmed, by Launay et al. [27] reported that on FDG PET/CT maximum standardized uptake values (SUV max) and adrenal to liver SUV max ratio were significantly higher in malignant tumors than adenomas, with results similar to Kunikowska et al.'s study [28]. By using 3.7 as a cutoff value for SUV max and 1.29 as a cutoff value for adrenal to liver SUV max, the sensitivity was 96.7%, and the specificity was 83.3% for distinguishing adrenal adenomas from malignant lesions.

In conclusion, adrenal glands can be affected by a wide spectrum of benign and malign lesions. Through the evaluation of different imaging modalities, it has become possible to differentiate benign and malign lesions non-invasively with a high accuracy rate. The diagnostic algorithm must be selected by considering the clinical histories and the laboratory results of patients.

Competing interests

The authors declare that they have no competing interests.

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